# Is response to anti-hepatitis C virus treatment predictive of mortality in hepatitis C virus/HIV-positive patients?

COHERE

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# Is response to anti–hepatitis C virus treatment predictive of mortality in hepatitis C virus/HIV-positive patients?


## The Hepatitis C Working Group for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord*



**Background:** Long-term clinical outcomes after hepatitis C virus (HCV) treatment of HIV/HCV patients are not well described. We aimed to compare the risk of all-cause and liver-related death (LRD) according to HCV treatment response in HIV/HCV patients in the multicohort study Collaboration of Observational HIV Epidemiological Research in Europe.

**Methods:** All patients who had started pegylated interferon + ribavirin (baseline) and followed for at least 72 weeks after baseline were included. Patients were categorized into three response groups depending on treatment duration and HCV-RNA measured in the window 24–72 weeks after baseline. Patients who received at least 24 weeks of therapy were defined as responders if their last HCV-RNA measured between 24 and 72 weeks after baseline was negative, and having 'unknown response' if HCV-RNA was unknown. Nonresponders were treated for less than 24 weeks or were HCV-RNA+ between 24 and 72 weeks after baseline. Mortality rates were compared using survival analysis, and Cox regression was used to compare hazard ratios of death between response groups.

**Results:** A total of 3755 patients were included: 1031 (27.5%) responders, 1639 (43.6%) nonresponders and 1085 (28.9%) with unknown response. Rates [per 1000 person-years of follow-up, 95% confidence interval (CI)] of all-cause death were 17.59 (14.88–20.78), 10.43 (7.62–14.28) and 11.00 (8.54–14.23) for nonresponders, responders and unknown responders, respectively. After adjustment, the relative hazard (nonresponders vs. responders) for all-cause death, LRD and nonliver-related death was 1.53 (95% CI 1.06–2.22), 3.39 (95% CI 1.32–8.75) and 1.22 (95% CI 0.80–1.84), respectively.

**Conclusion:** HIV/HCV patients with a favourable virological response to pegylated interferon + ribavirin had reduced risk of all-cause and LRD, whereas there was no difference in risk of nonliver-related death when comparing responders and nonresponders.





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**Keywords: hepatitis C virus, hepatitis C, HIV, interferon, mortality, ribavirin**


## Introduction

Treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) has until recently been the standard of care for treatment of hepatitis C virus (HCV) infection. Patients who achieve a sustained virologic response (SVR), that is they remain HCV-RNA-negative 6 months after end of HCV treatment, are considered virologically cured. An SVR has been shown to halt or reverse progression of liver fibrosis [1,2], but due to the slow evolution of liver disease in most patients, the clinical benefit of an SVR in terms of lower risk of liver-related


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complications and death may take several years to manifest. During that period, competing risk of death and risk of HCV reinfection could off-set some of the benefit of HCV therapy [3]. Furthermore, due to the numerous adverse effects and contraindications to interferon-based therapy, particularly in HIV-positive persons, HCV treatment was often not offered to those most in need of treatment [4]. Hence, an evaluation of the clinical benefit of HCV treatment requires a large study population and long-term follow-up.

In studies of HCV-monoinfected patients, it has been shown that achieving an SVR is associated with a lower risk of liver-related [5–8] and all-cause mortality [6,7]. The benefit is most pronounced for hepatic failure, and less so for risk of hepatocellular carcinoma (HCC).

In HIV/HCV-coinfected people, the long-term clinical outcome of HCV treatment has not been evaluated in prospective studies of unselected patients. In a mixed retrospective–prospective study from Spain, Berenguer *et al.* [9] found that nonresponders to HCV treatment had an almost nine-fold increased risk of liver-related clinical events compared with patients who achieved an SVR. Two subsequent studies from the same group found that coinfected patients who achieved an SVR also had a reduced risk of HIV progression and nonliver-related death [10] and risk of all-cause mortality and liver-related events among patients with METAVIR F2 fibrosis or less at the time of treatment initiation [11].

Compared with HCV-monoinfected patients, the benefit of HCV treatment could theoretically be either greater due to accelerated fibrosis progression in coinfected patients or lower due to differences in the prevalence of competing risk factors (both HIV-related and lifestyle factors) for mortality.

The objectives of our study were to compare the long-term risk of all-cause mortality and liver-related death (LRD) according to response to PEG-IFN/RBV in HIV/HCV-coinfected people enrolled in the large prospective multicohort study Collaboration of Observational HIV Epidemiological Research in Europe (COHERE).

## Methods

### Patients

COHERE (http://www.cohere.org) is a collaboration of 33 cohorts from across Europe and is part of the EuroCoord network (www.EuroCoord.net). COHERE was established in 2005 with the aim of conducting epidemiological research on the prognosis and outcome of HIV-positive persons, which the individual contributing cohorts cannot address themselves because of sample size or heterogeneity of specific subgroups of HIV-positive persons. Each cohort submits data using the standardized HIV Collaboration Data Exchange Protocol including information on patient demographics, HBV and HCV status and treatment, $CD4^+$ cell counts, use of cART, AIDS and deaths. Eighteen European cohorts provided data for the present analysis. Our analyses were based on data merged in July 2013.

All HCV-infected patients in COHERE who had ever started PEG-IFN/RBV and who were followed up for at least 72 weeks after treatment initiation were included. Baseline is defined as the date of HCV treatment initiation, whereas time T0 is the date 72 weeks after treatment initiation. During most of the study period, 48 weeks of HCV treatment was standard of care for coinfected patients. The earliest time point at which SVR24 can be assessed would be 72 weeks after treatment initiation for most patients.

### Definitions of hepatitis C virus treatment response

Follow-up HCV-RNA values were not reported for all patients after end of therapy. We therefore categorized patients into three different HCV treatment response groups depending on HCV treatment duration and HCV-RNA results measured in the window 24–72 weeks after baseline. Patients who received at least 24 weeks of IFN/RBV were defined as 'responders' if their latest HCV-RNA measured in the window 24–72 weeks after baseline was negative, and having 'unknown response' if they had no HCV-RNA measured in the week 24–72 window. Patients were defined as 'non-responders' if they had received less than 24 weeks of HCV therapy or if their latest HCV-RNA measured the week 24–72 window after baseline was positive. To define positive HCV-RNA values, both qualitative (+/−) and quantitative measures (>615 IU/ml) were used.

### Biomarkers of fibrosis

Levels of fibrosis were determined in the time window (−6; 0) months prior to initiation of HCV treatment by measurement of the aspartate aminotransferase-to-platelet ratio index (APRI) [$100 \times$ (aspartate aminotransferase/upper limit of normal)/platelet count ($10^9$/l)]. Significant fibrosis ($\geq$F2 on the METAVIR scale) and cirrhosis were defined as APRI more than 1.5 and APRI more than 2.0, respectively [12].

### Statistical methods

Main characteristics of the patients are described and compared according to whether a person was classified as responder, nonresponder or unknown response using chi-square or nonparametric Kruskal–Wallis tests as appropriate.

Three different endpoints were analysed: all-cause mortality, LRD and nonliver-related death. Causes of death were adjudicated individually by the participating cohorts in COHERE. Incidence rates were calculated as number of deaths divided by person-years of follow-up (PYFU) at risk. Confidence intervals (CIs) around these estimates were calculated assuming a Poisson distribution. Mortality rates in the three groups were compared using standard survival analysis. Survival times accrued from the time T0 up to the date of death or last available follow-up. In the analysis of time to cause-specific death, people who died for other reasons were censored administratively at the date of last follow-up according to a competing-risk approach to analysis. People who died between baseline and T0 were excluded. Kaplan–Meier plots have been used to compare the cumulative risk of survival in the three exposure groups (responders, nonresponders and unknown response to IFN/RBV). Univariable and multivariable Cox regression models were used to compare hazard ratios of death between these groups after controlling for a number of prespecified confounders. We used a manual build-up of the multivariable models adjusting sequentially for subset of time-fixed confounders measured at the time of IFN/RBV initiation and grouped according to common features (e.g. demographics, HIV-related factors and HCV-related factors). We only included in these sets of potential confounders factors that have been previously described to be a common cause of treatment initiation and risk of death, that is age, sex, origin, year of baseline, mode of HIV transmission, prior AIDS, current $CD4^+$ cell count, $CD4^+$ nadir, HIV RNA, HIV treatment at T0, HBsAg and APRI.

## Results

### Baseline characteristics

We included a total of 3755 patients, who had started HCV treatment and had at least 72 weeks of follow-up after treatment was started (Fig. 1). Fifty-two patients had died between the date of HCV treatment start and week 72 (T0) of follow-up. Median [interquartile range (IQR)] duration PEG-IFN/RBV treatment was 9 (5–12) months. Among included patients, 1031 (27.5%) were responders, 1639 (43.6%) were nonresponders and 1085 (28.9%) had unknown HCV treatment response. Compared with nonresponders, responders started HCV treatment later (2007 vs. 2005), were more likely to be MSM (31 vs. 12%) and HBsAg-positive (4.5 vs. 2.6%), had higher $CD4^+$ cell count (455 vs. 405 cells/μl), lower HCV-RNA levels (5.85 vs. 6.03 $\log_{10}$ IU/ml), less likely to be woman (20 vs. 25%) and have a prior AIDS diagnosis (22 vs. 27%). The median APRI score was slightly higher among responders (0.9 vs. 0.8) (Table 1).

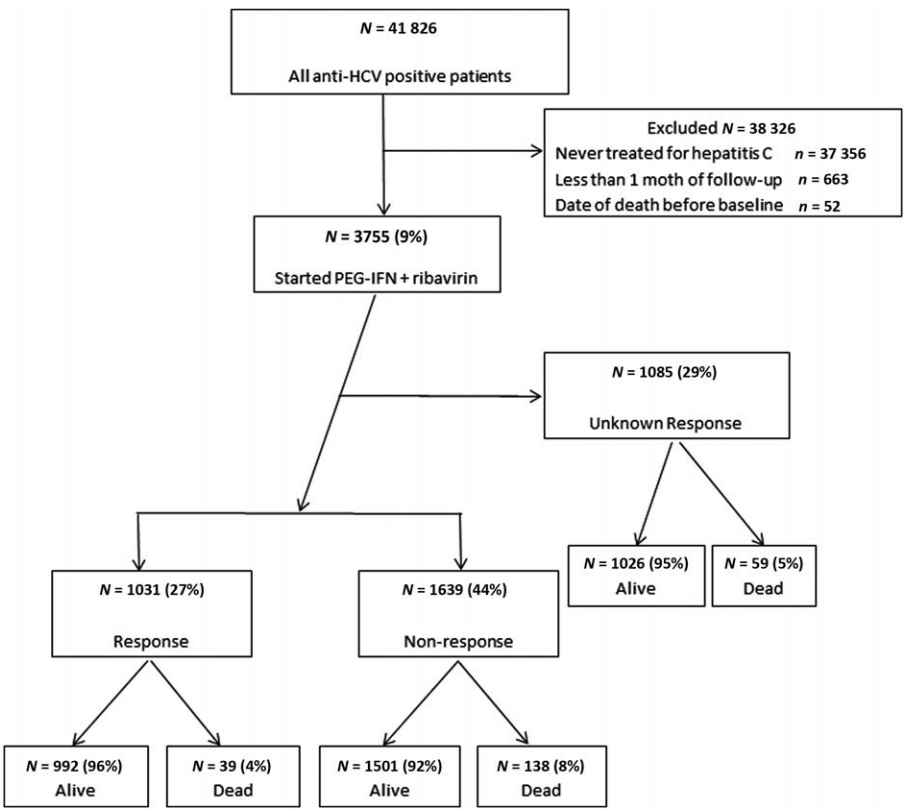


**Fig. 1. Selection of patients.**

Among patients with available data, the prevalence of cirrhosis, defined as APRI more than 2.0, was 16.0% in those with unknown response (104/650), 20.0% in nonresponders (200/999) and 26.7% in responders (182/681). There were no differences between the response groups in time from baseline to assessment of APRI.

### All-cause mortality according to hepatitis C virus treatment response

After a median of 4.0 (IQR 2.0–6.5) years of follow-up from T0, a total of 236 deaths had occurred. One hundred and thirty-eight (8.4%) of HCV treatment nonresponders had died vs. 39 (3.8%) deaths among responders and 59 (5.4%) with unknown HCV treatment response. The rates (per 1000 PYFU, 95% CI) of all-cause death were 17.59 (14.88–20.78), 10.43 (7.62–14.28) and 11.0 (8.54–14.23) for nonresponders, responders and unknown responders, respectively.

Figure 2 shows a Kaplan–Meier plot of the cumulative risk of all-cause mortality. For nonresponders, the 7-year risk (95% CI) of all-cause death was 11.6% (9.5–13.7), whereas the 7-year risk was significantly lower for responders 8.0% (5.1–10.8) and for patients with unknown treatment response 7.8% (5.6–10.1).

In the unadjusted Cox regression analysis, nonresponders had a relative hazard of 1.64 (95% CI 1.15–2.34) for all-cause death compared with responders. Results were similar after adjusting for demographics, HIV-related (prior AIDS, on cART at T0, current HIV-RNA and $CD4^+$ cell count) and hepatitis-related factors (HBsAg and APRI) in separate models (Fig. 3). In the fully adjusted analysis, the relative hazard (nonresponders vs. responders) for all-cause death was 1.53 (95% CI 1.06–2.22). In all analyses, the relative hazard for all-cause death was NS when comparing responders with unknown responders.

### Liver-related mortality according to hepatitis C virus treatment response

LRD accounted for a third of all deaths among nonresponders 48 of 139 (34.8%), but only 12.8% (5/39) among responders and 22.0% (13/59) among patients with unknown response. The rates (per 1000 PYFU, 95% CI) of LRD were 6.12 (4.61–8.12), 1.34 (0.56–3.21) and 2.40 (1.41–4.18) for nonresponders, responders and unknown responders, respectively.

Among the five responders who died from LRD, two had a baseline APRI score indicating cirrhosis, one had significant fibrosis and two had no information about fibrosis level. One patient had evidence of HCV reinfection, whereas the four other remained HCV-RNA-negative during follow-up. None were diagnosed with HCC.

The differences in risk of LRD between responders and nonresponders were more pronounced than for all-cause death, but the CIs were quite wide reflecting the relative low number of LRDs in each group. The 7-year cumulative risk of LRD was significantly higher for nonresponders (4.2%, 95% CI 2.9–5.5) compared with the risk for responders (1.6%, 95% CI 0.0–3.3) and for patients with unknown treatment response (1.4%, 95% CI 0.4–2.4) (Fig. 4).

In the unadjusted Cox regression analysis, nonresponders had a 4.43 (95% CI 1.76–11.14) increased risk of LRD compared with responders. Again, when adjusting for demographic, HIV-related and hepatitis-related factors, there was little change in the incidence rate ratios (Fig. 5). In the fully adjusted analysis, the relative hazard (nonresponders vs. responders) of LRD was 3.39 (95% CI 1.32–8.75).

### Nonliver-related mortality according to hepatitis C virus treatment response

A total of 34 and 90 nonliver-related deaths occurred among responders and nonresponders, respectively. In both groups, non-HCC malignancy was the predominant cause of death (5/34 and 16/90, respectively) followed by 'unknown cause' (5/34 and 16/90, respectively). Four nonresponders died from AIDS, whereas there were no AIDS-related deaths in the responder group. To investigate whether a positive HCV treatment outcome also results in a lower risk of nonhepatic mortality, we repeated the analyses excluding all LRDs. In the unadjusted analysis, there was no difference (nonresponders vs. responders) in incidence of nonliver-related death (hazard ratio 1.23, 95% CI 0.83–1.83). Results were similar after adjustment for demographic factors (1.19, 95% CI 0.79–1.78), HIV-related factors (1.22, 95% CI 0.81–1.82) and APRI and HBsAg status (1.35, 95% CI 0.91–2.01). In the fully adjusted model, the relative hazard was (1.22, 95% CI 0.80–1.84). Similarly, there was no difference when comparing responders with patients with unknown response (results not shown).

## Discussion

In this large prospective study, we included 3755 HIV/HCV-coinfected patients, who had received PEG-IFN/RBV. After a median of 4.0 years follow-up from week 72 after treatment initiation, we found that patients who had a favourable treatment response had a significantly improved all-cause and liver-related mortality compared with patients who were nonresponders. Our findings confirm the survival benefit of an SVR, shown in previous studies of HCV-monoinfected [6,7] and HIV/HCV-coinfected patients [9,13]. However, compared with these studies, the improved survival in our study was relatively modest (hazard ratio 1.53 for comparing responders with nonresponders). In the Spanish study by Berenguer *et al.* [9], which is the only other large

**Table 1. Patient characteristics at the date of hepatitis C virus treatment initiation.**

| Characteristics | Responders, $N=1031$ | Nonresponders, $N=1639$ | Unknown response, $N=1085$ | $P$ value[a] | Total, $N=3755$ |
|---|---|---|---|---|---|
| Age, median years (IQR) | 42 (37, 46) | 42 (37, 46) | 41 (37, 46) | 0.672 | 42 (37, 46) |
| Female, $N$ (%) | 210 (20.4%) | 401 (24.5%) | 245 (22.6%) | 0.048 | 856 (22.8%) |
| Year of treatment initiation, median (IQR) | 2007 (2005, 2009) | 2005 (2003, 2008) | 2005 (2003, 2008) | <0.001 | 2006 (2003, 2008) |
| Region of birth, $N$ (%) | | | | 0.002 | |
| Europe | 789 (83.2%) | 1328 (87.8%) | 820 (82.6%) | | 2937 (85.1%) |
| Other | 83 (8.1%) | 127 (7.7%) | 92 (16.1%) | | 302 (8.0%) |
| Unknown | 159 (16.8%) | 184 (12.2%) | 173 (17.4%) | | 516 (14.9%) |
| Mode of HIV transmission, $N$ (%) | | | | <0.001 | |
| MSM | 322 (31.2%) | 211 (12.9%) | 130 (12.0%) | | 663 (17.7%) |
| Heterosexual contact | 133 (12.9%) | 216 (13.2%) | 169 (15.6%) | | 518 (13.8%) |
| Injecting drug use | 467 (45.3%) | 1049 (64.0%) | 693 (63.9%) | | 2209 (58.8%) |
| Other/unknown | 109 (10.6%) | 163 (9.9%) | 93 (8.6%) | | 365 (9.7%) |
| Prior AIDS diagnosis, $N$ (%) | 226 (21.9%) | 443 (27.0%) | 254 (23.4%) | <0.001 | 923 (24.6%) |
| On ART, $N$ (%) | 864 (83.8%) | 1429 (87.2%) | 927 (85.4%) | 0.048 | 3220 (85.8%) |
| $CD4^+$ cell count, median (IQR) (cells/μl) | 455 (180, 656) | 405 (170, 582) | 447 (248, 627) | <0.001 | 423 (200, 619) |
| HIV-RNA, median (IQR) ($\log_{10}$ copies/ml) | 3.01 (1.96, 4.34) | 3.04 (1.72, 4.14) | 2.97 (1.90, 4.13) | 0.383 | 3.01 (1.84, 4.17) |
| HCV RNA, median (IQR) ($\log_{10}$ IU/ml) | 5.85 (5.11, 6.34) | 6.03 (5.51, 6.60) | 5.98 (5.53, 6.51) | <0.001 | 5.95 (5.35, 6.51) |
| HCV genotype 1, $N$ (%)[a] | 274 (26.6%) | 371 (22.6%) | 158 (14.6%) | <0.001 | 803 (21.4%) |
| HBsAg-positive, $N$ (%)[b] | 46 (3.8%) | 42 (5.4%) | 29 (4.2%) | <0.001 | 117 (4.4%) |
| Haemoglobin, median (IQR) (g/dl) | 15 (12, 16) | 15 (13, 16) | 15 (14, 16) | 0.046 | 15 (13, 16) |
| Platelet count, median (IQR) ($10^9$/l) | 168 (123, 216) | 171 (124, 221) | 178 (131, 229) | 0.006 | 173 (126, 222) |
| ALT, median (IQR) (IU/l) | 95 (51, 164) | 71 (44, 121) | 71 (44, 112) | <0.001 | 71 (44, 112) |
| AST, median (IQR) (IU/l) | 65 (41, 122) | 59 (39, 95) | 55 (37, 85) | <0.001 | 60 (39, 100) |
| APRI score, median (IQR)[c] | 0.9 (0.5, 2.2) | 0.8 (0.5, 1.7) | 0.8 (0.5, 1.4) | <0.001 | 0.8 (0.5, 1.7) |

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; ART, antiretroviral therapy; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.
[a]$N$ with data: 1437.
[b]$N$ with data: 2653.
[c]$N$ with data: 2330.

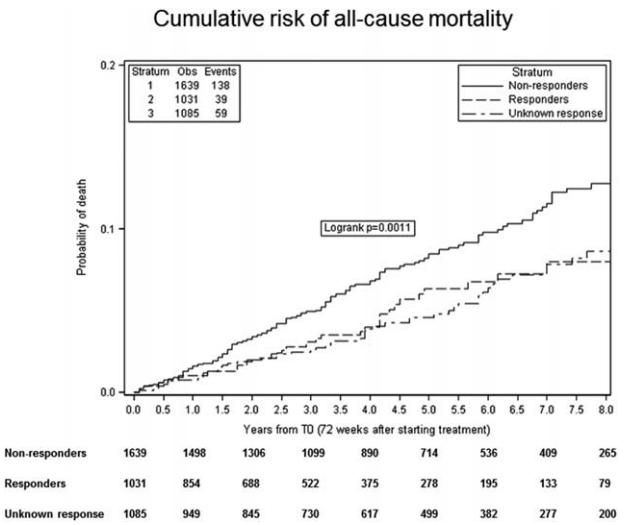


**Fig. 2. Cumulative risk of all-cause mortality in the three hepatitis C virus treatment response groups.**

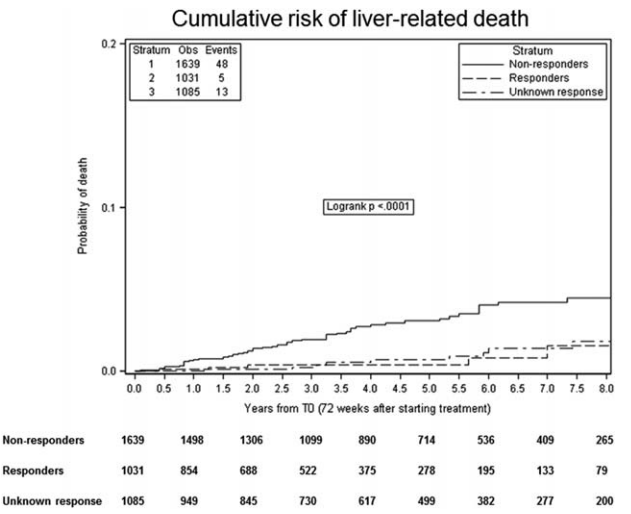


**Fig. 4. The figure shows the cumulative risk of liver-related death in the three hepatitis C virus treatment response groups.**

observational study to include HIV/HCV-coinfected patients from routine clinical practice, the incidence of all-cause mortality among patients with SVR was lower compared with the incidence among responders in our study (0.46 vs. 1.04 per 100 PYFU), whereas the all-cause mortality was higher among nonresponders in their study (3.12 vs. 1.76 per 100 PYFU). The excess all-cause mortality among nonresponders in the Spanish study seems to be mainly explained by a high prevalence (39%) of patients with advanced fibrosis or cirrhosis, resulting in a high incidence of LRD among nonresponders compared with the incidence among nonresponders observed in our study (1.65 vs. 0.61 per 100 PYFU).

In our study, only five out of 37 deaths in the treatment response group were from liver-related causes, and none of them due to HCC. Two of the five patients had evidence of cirrhosis at the time of treatment initiation, whereas one had evidence of HCV reinfection. Other studies have documented, that although an SVR reduces the risk, liver-related complications can occur several years after SVR. This is particularly the case with HCC in patients with cirrhosis at the time of treatment [6,14]. Longer follow-up of our cohort is warranted to determine whether the incidence of HCC and other liver-related clinical events remains low for patients with treatment response.

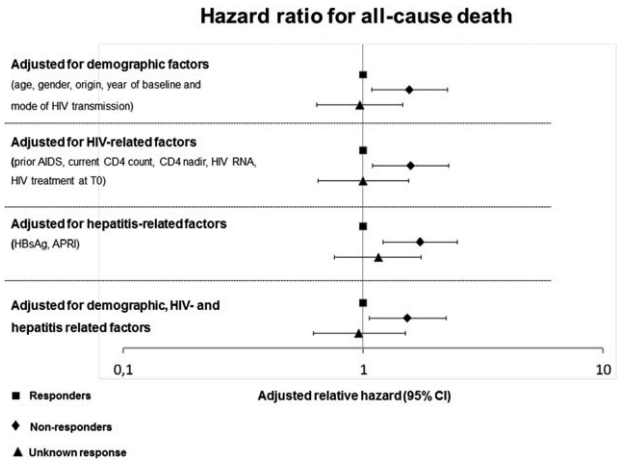


**Fig. 3. Adjusted hazard ratio for all-cause mortality according to hepatitis C virus treatment response.** Adjustments were made for prespecified demographic-related, HIV-related and hepatitis-related factors in three separate Cox regression models as well as for all factors combined.

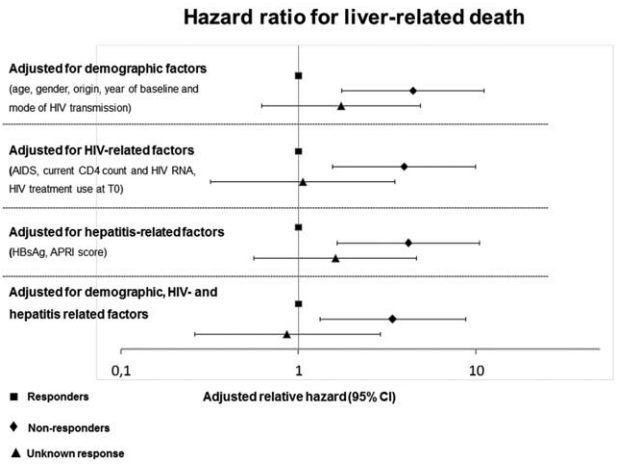


**Fig. 5. The figure shows the adjusted hazard ratio for liver-related death according to hepatitis C virus treatment response.** Adjustments were made for prespecified demographic-related, HIV-related and hepatitis-related factors in three separate Cox regression models as well as for all factors combined.

As interferon is contraindicated in patients with advanced cirrhosis due to the risk of liver decompensation, it is likely that patients with more advanced liver disease, who would have gained more clinical benefits from HCV eradication, were excluded. It is therefore conceivable that with the new tolerable and effective interferon-free direct-acting antivirals (DAA), we will be able to prevent more liver-related and, possibly, nonliver-related complications, and this should be addressed in further observations. Although interferon-based therapy is no longer standard of care, the data presented in this article are still of relevance to inform the prognosis for the many patients who were treated and cured with interferon before the arrival of DAA. Furthermore, interferon-based therapy is still commonly used in some countries that cannot afford the market price of DAA. In addition, consequences of cure are likely to be similar regardless of which treatment was used to achieve success.

The link between chronic HCV infection and different autoimmune and lymphoproliferative conditions, for example mixed cryoglobulinaemia and some types of lymphoma, is well established [15]. There is also emerging evidence of an association between HCV infection and risk of cardiovascular disease and other extrahepatic diseases [15–17]. If the association is causal, one would expect a decrease in risk of nonliver-related death after SVR. In our study, we did not find a lower risk of nonliver-related death among those with a favourable HCV treatment response. This is in contrast to a national Spanish study that found a three-fold lower risk of nonliver-related death in HIV/HCV-coinfected patients with SVR compared with patients who did not achieve an SVR [10]. The reason for this difference is not clear, but with only five and 32 nonliver-related deaths among patients with and without SVR, respectively, the study had limited power to investigate the question. It is possible that some of the apparent extrahepatic health benefit of an SVR is related to behavioural differences after treatment and not the treatment outcome *per se*, as demonstrated by a Scottish observational study of HCV-monoinfected patients in which patients who achieved SVR after interferon-based therapy had lower risk of hospitalization for alcohol intoxication and violence-related injury after treatment compared with nonresponders to HCV treatment [18]. These findings should be explored in other cohorts and in patients undergoing DAA therapy.

The major strengths of this analysis are the large number of coinfected patients recruited from a diverse geographical area throughout Europe, the long prospective follow-up after HCV treatment and our ability to adjust for relevant risk factors for all-cause and LRD. However, like in all observational studies, there remains the possibility of unmeasured confounding. Another limitation is the lack of follow-up HCV-RNA measurements on all patients at least 6 months after end of therapy. In addition, some of the patients categorized as responders could have had HCV-RNA relapse, and some patients categorized as nonresponders could have achieved an SVR. However, this limitation would only tend to underestimate the survival benefit of HCV therapy. Unexpectedly, the prevalence of cirrhosis, as determined by the APRI score, was higher among responders than among nonresponders. Data to calculate the APRI score were only available for 66 and 61% of responders and nonresponders, respectively. If the reason for not having an APRI score is associated with disease status, selection bias could have been introduced.

In conclusion, we have shown that among HIV/HCV-coinfected patients, a favourable virological response to HCV treatment is associated with reduced risk of both LRD and improved overall survival in the interferon era. Whether this holds true with the new direct-acting antivirals remains to be investigated.

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## Conflicts of interest

There are no conflicts of interest.

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